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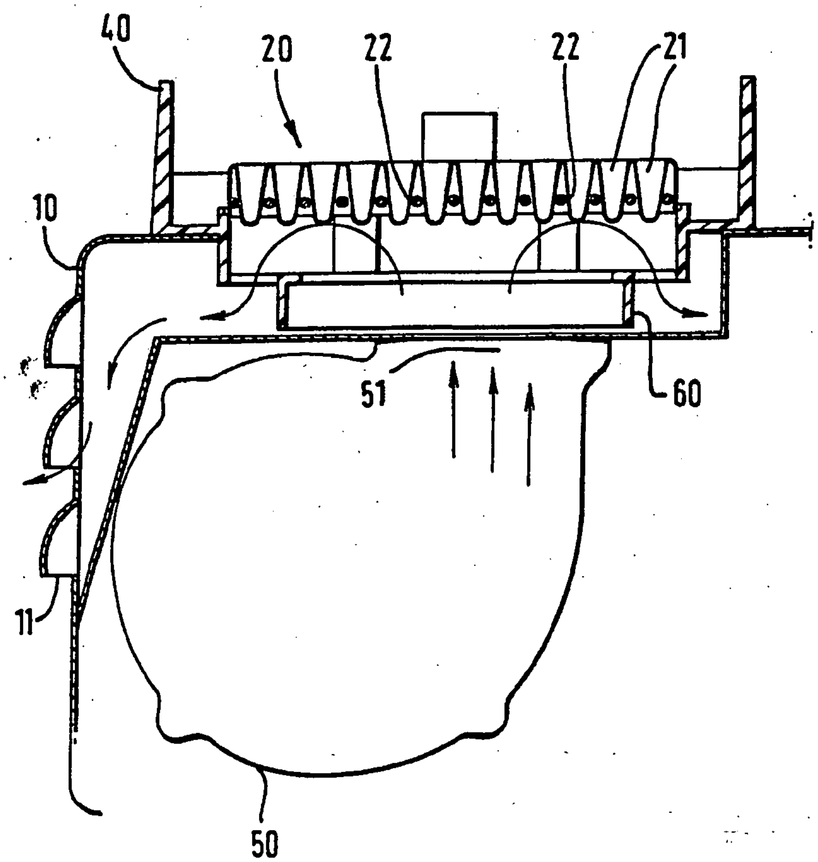
(54) Title: REACTION TEMPERATURE CONTROL DEVICE

(57) Abstract

A temperature control device comprises a heater block (20) that is formed from a continuous layer of metal that is heated by conduction by a heater element (22) in thermal contact with the block, and cooled by a fan (50) under the block. The upper surface of the block may have flat areas to accommodate samples on microscope slides or have recesses (21) to hold samples in small test tubes.



*LEDIGLICH ZUR INFORMATION*

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# Reaction Temperature Control Device

The present invention relates to temperature control devices, and in particular to devices for controlling the temperature of substances undergoing chemical reaction.

Many chemical reactions, in particular biochemical reactions, require the temperature of the reacting mixture to be controlled within close limits during the reaction to ensure the requisite yield and purity of product. It may also be necessary to vary the reaction temperature according to a predetermined temperature profile during the reaction. Two particular types of reaction that require close, variable temperature control are polymerase chain reactions (PCR) and Ligase chain reactions (LCR). In the case of the latter heating at a set temperature lasts for only 5-10 seconds before a new heating temperature must be selected. Such stringent criteria require the temperature control device to be able to heat and cool the reaction mixture very quickly and very accurately.

Such a temperature control device is described in International Patent Application No. WO/PCT/GB89/00323 (DEAN and EVANS). This Application discloses a device for controlling the temperature of a plurality of samples of a reacting mixture, comprising a heater block for receiving said samples, means for heating the block, means for cooling the block by forced convection, and temperature sensing means to monitor the temperature of one or more samples and signal a controller which controls the means for heating and the means for cooling to regulate the sample temperature.

The block is heated by a quartz-halogen lamp directly below the block which gives out radiant heat. This is directional and because of this the heating of the block is not always uniform. This can result in hot spots and limits the number of samples the device can hold.

Accordingly, a first aspect of the invention provides a device for controlling the temperature of a plurality of samples of a reacting mixture, comprising a heater block for receiving said samples, means for heating the block, means for cooling the block by forced convection, and temperature sensing means to monitor the temperature of one or more samples and signal a controller which controls the means for heating and the means for cooling to regulate the sample temperature, characterised in that the means for heating the block comprise one or more heater elements positioned in thermal contact with the block so that heat transfer between the element(s) and the block is substantially by conduction.

This provides even heating of the samples.

The known device is cooled by a fan under the block. The location of the lamp means that the fan must be positioned to one side of the block. This causes uneven cooling of the test tubes.

In a preferred arrangement of the first aspect of the invention, the means for cooling the block by forced convection comprises a fan that is positioned under the centre of the block.

Such symmetrical positioning ensures even cooling of

the samples.

In the known device the block is made from a drilled sheet of copper in which copper tubes are soldered. This makes the block difficult and expensive to construct. Furthermore the soldered joints can disrupt heat conduction.

Preferably, in the first aspect of the invention the block is made of solid metal.

This further ensures even heat distribution. The block can be easily made by electroforming .

The known device uses thermocouples which limits the accuracy of the temperature control and necessitates periodic recalibration of the controller.

Preferably, in the first aspect of the invention the temperature sensing means comprises one or more thermistors.

In order that the invention and its various other features may be understood more easily, embodiments thereof will now be described by way of example only, with reference to the drawings, wherein:-

Fig.1 is a vertical section through a control device according to a first embodiment of the present invention;

Fig.2 is a horizontal section through a part of the heater block comprising part of the first embodiment; and

Fig.3 is a vertical section through a second embodiment of the invention.

The device comprises a casing 10, a rectangular heater block 20, a heater block support 40, a fan 50, and a collar 60. The device further comprises a controller and temperature sensing means which are not shown in the drawings.

The heater block 20 is electroformed and comprises a single continuous layer of silver. The block contains ninety six recesses 21 into which small test tubes (not shown in drawings) containing the reactant mixture are inserted. The recesses form projections on the underneath of the block. The arrangement of the recesses conforms with that of a standard size ninety six well microtitre dish (126 mm x 86 mm nominal).

The heater block 20 is heated by a serpentine electric element 22 that extends between the recesses. The element winds back and forth along the rows of recesses 21. The element 22 is formed from a sheathed conductor.

The underside of the heater block 20 is cooled by a fan 50. The outlet 51 of the fan is directed towards the centre underneath the heater block.

The heater block 20 is supported by the heater block support 40 which is plastic and which is supported by the casing 10. The plastic collar 60 forms part of and hangs from the support 40.

The device is controlled by a controller that is responsive to two thermistor units placed one in

thermal contact with the recesses 21 underneath the block, and another in a, dummy test tube within a recess.

The device, particularly the support 40 and collar 60, is configured to provide an even airflow over the base of the heater block 20, to ensure uniform cooling of the samples. The airflow path is indicated by arrows in Fig.1. Louvres 11 are provided in the casing 10 to allow hot air to escape.

The device is particularly suited to undertaking biochemical reactions. The reactant samples are contained in polypropylene sample tubes which each contain a sample of about 100 microtitres. The tubes are inserted into the recesses and can be filled in situ using a multiheaded pipette. The device can achieve block heating and cooling rates of $3^{o}C$/sec and $2^{o}C$/sec respectively, which correspond to a sample heating or cooling rate of $1.2^{o}C$/sec.

The degree of control of the device allows it to perform ligase chain reactions.

The sample tubes can be made in glass. This enhances heat transfer to the samples.

The sample tubes can be replaced with sealed 0.5 microlitre microfuge tubes. As these are larger than the standard sample tubes, only every other recess is used.

The device shown in Fig.3 is for heating samples that are held on microscope slides. Each sample is held between a slide 70 and a cover 71.

The device comprises two heater blocks 80, each comprising a continuous sheet of metal 81 that is supported by a casing 84 and that is overlaid by a serpentine electric element 82. A flat sheet of aluminium 83 lies over each element and it is on this that the slides 70 lie.

The slides 70 are covered by a housing 90 that is used to place samples on the blocks 80 for heating and remove them after heating. The housing comprises edge support members 91 that engage the ends of the slides when the housing is lifted. The edge support members define two rectangular apertures in plan view which can each support a number of slides. Each aperture contains locating means (not shown in Fig.3) which ensure the slides are kept in a regular arrangement and do not move about. The structure of the housing is completed by a lid member 92 having a support 93. The whole structure forms a humidity chamber when the lid member 91 is in place.

To use the device the operator first loads the housing 90 whilst it is removed from the frame 84. A number of housings can be loaded in preparation for sample heating. As the housing is lowered over the device the slides 70 become supported on the aluminium sheets 83. The housing is further lowered until the lid member 92 rests on the edge of the casing 84 in the position shown in Fig.3. The samples are then heated in the required manner. When heating is completed the housing is lifted away from the casing and the slides 70 removed.

In both embodiments of the invention the type of heating element 22 can be varied. A plurality of elements can replace the serpentine element. A woven conductive cloth can be incorporated in the heater block.

A number of modifications can be made to the devices described. A number of devices can be incorporated into a single unit for dealing with a larger number of samples. In a particular embodiment a single unit incorporates four heating blocks of the type described. All four blocks are controlled by a single controller but measurements are only taken from a single heating block as representative of all the blocks. Such a unit is only workable because of the high degree of uniformity achievable in the heating of each block.

The devices have many advantages over known devices. In particular, the temperature of different samples at different positions cross the heater block 20 have a high degree of uniformity. The effect of this is to improve the uniformity of product from the sample tubes. This in turn allows more samples to be accommodated in a single heater block (ninety six compared with seventy two in the cited prior device). This also reduces the energy consumption of the device.

The uniformity of heating to the sample tubes is also enhanced by making the heater block in silver, which has a high thermal conductivity, and by employing a jointless construction. The use of a solid silver block rather than a soldered copper block enhances heat transfer through the block. By eliminating the difficult soldering operations the cost of the block is reduced.

Incorporating the heating means into the heater block, rather than using a radiant heater, allows the fan to be positioned under the centre of the block. This results in an even airflow pattern over all parts of the block. The configuration of the airflow path eliminates dead spots where the cooling effect would be reduced.

The use of thermistors for temperature sensing rather than thermocouples increases the accuracy of operation and eliminates the need to periodically recalibrate the controller.

## CLAIMS

1. A device for controlling the temperature of a plurality of samples of a reacting mixture, comprising a heater block (20) for receiving said samples, means for heating the block, means (50) for cooling the block by forced convection, and temperature sensing means to monitor the temperature of one or more samples and signal a controller which controls the means for heating and the means for cooling to regulate the sample temperature, characterised in that the means for heating the block comprise one or more heater elements (22) positioned in thermal contact with the block so that heat transfer between the element(s) and the block is substantially by conduction.

2. A device according to claim 1, wherein the means for cooling the block (20) by forced convection comprises a fan (50) that is positioned under the centre of the block.

3. A device according to claims 1 or 2, wherein the block (20) is made of solid metal.

4. A device according to any preceding claim, wherein the temperature sensing means comprise one or more thermistors.

5. A device according to any preceding claim, wherein the means for heating the block (20) comprises one or more elongate heating elements (22) following a sinuous path.

6. A device according to any of claims 3 to 5, wherein the block (20) is silver.

7. A device according to any preceding claim, wherein the heater block (20) contains a plurality of recesses (21).

8. A device according to claim 7, wherein the samples are contained in reaction vessels which are placed in the recesses.

9. A device according to claims 7 or 8, wherein the device can heat or cool a 100 microlitre sample of biological reactant material at a rate of 1.2°C/second.

10. A device according to any of claims 7 to 9, wherein the device allows ligase chain reaction to be undertaken in the samples.

11. A device according to any of claims 1 to 6, wherein the top of the heater block has a flat area for receiving the samples.

12. A device according to claim 11, wherein the samples are held on microscope slides.

13. A device for controlling the temperature of a plurality of samples of a reacting mixture, comprising a heater block (20) having a plurality of recesses (21) for receiving said samples, a heater element (22) in thermal contact with the block, means (50) for cooling the block by forced convection, and temperature sensing means to monitor the temperature of one or more of said samples and signal a controller which controls the heater element and the forced convection means to regulate the sample temperature, characterised in that the heater block comprises a continuous layer of metal.

FIG. 1

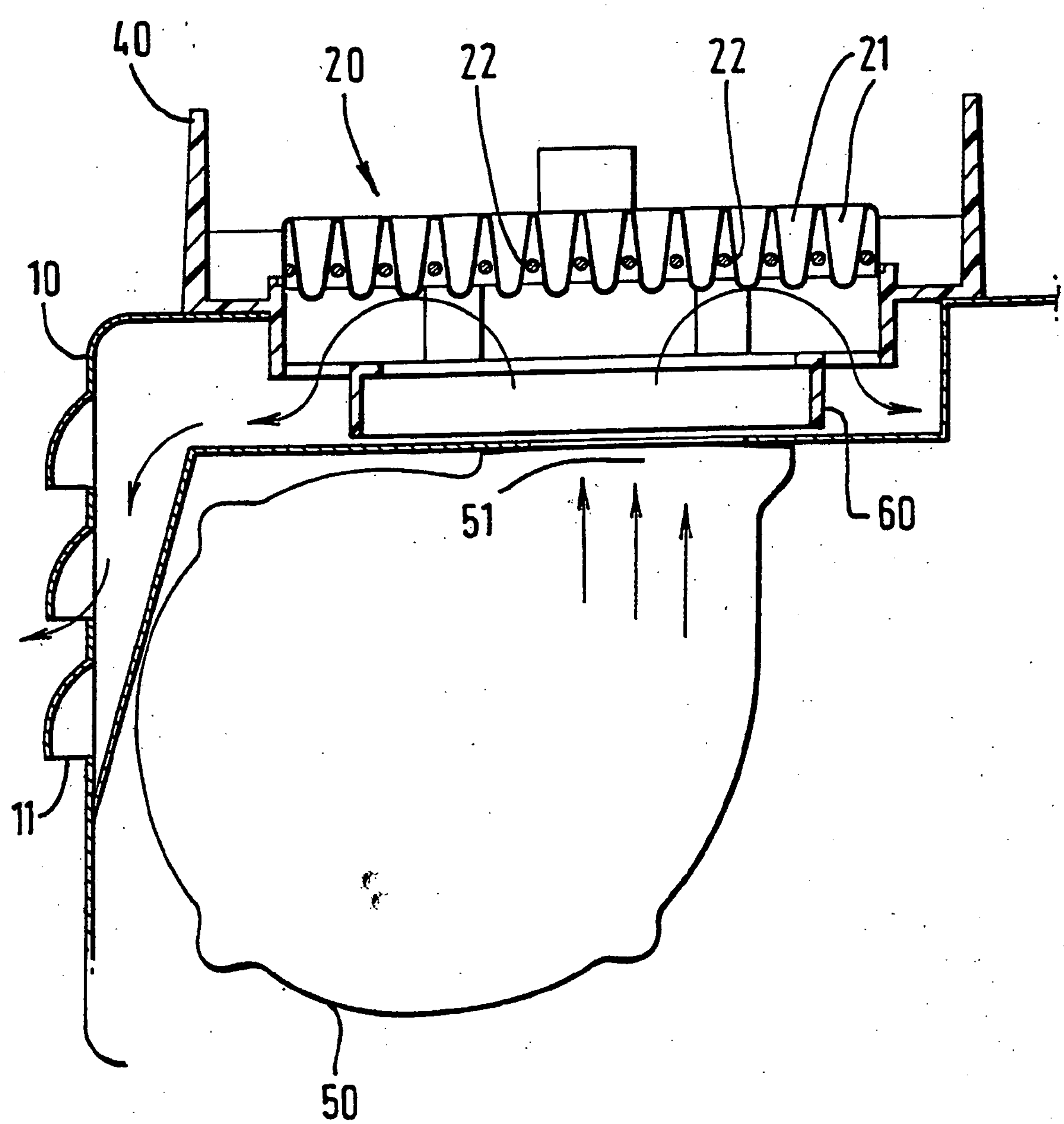


FIG. 2

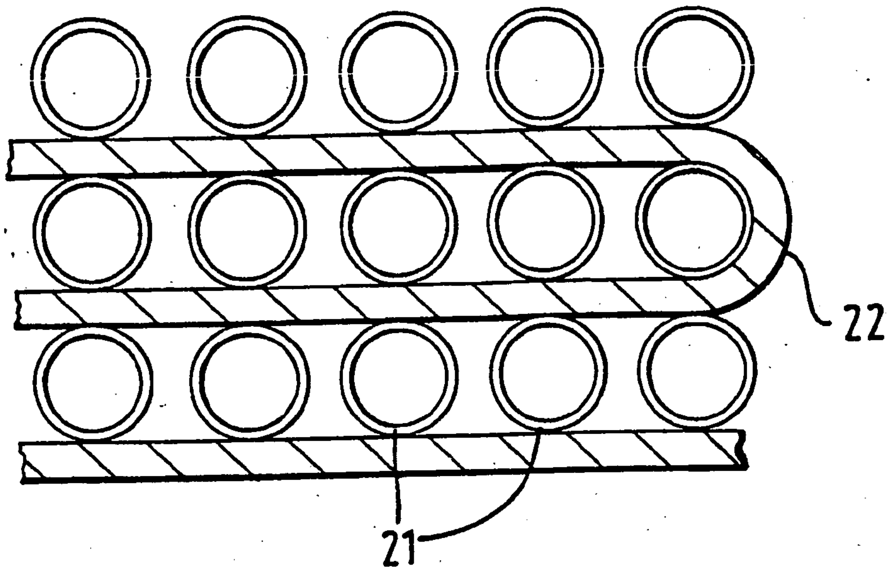
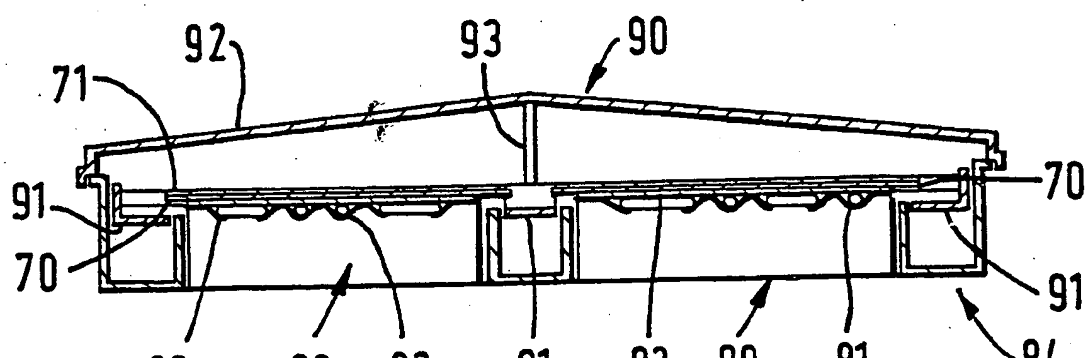



FIG. 3



**I. CLASSIFICATION OF SUBJECT MATTER** (if several classification symbols apply, indicate all)[6]

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Int.Cl. 5 G05D23/19; B01L7/00

**II. FIELDS SEARCHED**

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

**III. DOCUMENTS CONSIDERED TO BE RELEVANT**[9]

| Category° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | WO,A,8 909 437 (DEAN AND EVANS) 5 October 1989 cited in the application see the whole document | 1,3,7,13 |
| Y | | 2,9,10 |
| A | | 4-6,8, 11,12 |
| Y | US,A,4 865 986 (COY ET AL.) 12 September 1989 see column 1, line 7 - column 2, line 12 see column 3, line 47 - column 4, line 27; figure 4 | 2,9,10 |
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# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9201996
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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